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CASE REPORT article

Switch from once-daily tacrolimus (Advagraf) to twice-daily immediate-release tacrolimus (Prograf) in liver transplantation: Case study

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Abstract: Tacroclimus is an immunosuppressive drug widely used for the prevention of rejection in organ transplants. It is marketed in two forms: Prograf administered twice a day, and Advagraf, which allows only one administration per day. Advagraf is often used in liver transplantation. Through this clinical case, we demonstrate the role of therapeutic drug monitoring in dosage optimization during the switch to tacrolimus from the Advagraf form to the Prograf form. This is a 60-year-old patient who underwent liver transplantation in 2014, treated with Advagraf 2.5 mg once in the morning. The residual CO concentration was 7.0 ng/ml. Due to the unavailability of Advagraf, this drug was switched to Prograf at the same dosage, 2.5 mg/d in two doses (1.5 mg in the morning and 1.0 mg in the evening). Co increased from 7.0 to 11.0 ng/ml, AUC was 194 ng.h/ml [120-150]. When substituting Advagraf for Prograf, C0 monitoring should be regular and close, and dosage adjustments should be made to ensure that a similar systemic exposure is maintained.

Introduction

Tacrolimus (Tac) and cyclosporine are immunosuppressive drugs (IS), calcineurin inhibitors (CNIs) which are widely used in solid organ transplantation, particularly in liver transplantation (LT). In LT, Tac is the first-line IS treatment for rejection prophylaxis. Compared to cyclosporine A, Tac reduces the incidence of acute rejection, graft loss and one-year mortality [1]. Tac was originally available as an Immediate Release Tac (IR-Tac) formulation (Prograf) given twice a day. To improve patient adherence to treatment and reduce inter- and intra-individual variability, an Extended-Release Tac (ER-Tac) formulation has been developed and administered once daily (Advagraf) [2]. There are no significant differences in terms of efficacy and toxicity between the two formulations [2]. However, Tac IR-TAC and ER-TAC are not bioequivalent and they should not be substituted without careful therapeutic drug monitoring [3]. The objective of this work is to demonstrate through a case report the role of the Therapeutic Drug Monitoring (TDM) in dosage optimization during the switch tacrolimus from the ER-TAC once-a-day dose to the IR-Tac twice-daily dose.

Case report: On June 07th, 2020, a 60-year-old patient was admitted to the Pharmacovigilance Department of the Hospital and University Establishment of Oran (HUEO), in Algeria, for TDM of Tac. She underwent a

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cadaveric liver transplant on May 03th, 2014. Her medical history was asthma, open-angle glaucoma, anemia, and HIV positive. After LT, she developed high blood pressure and insulin-dependent type 2 diabetes. Its immunosuppressive treatment was ER-Tac 2.5 mg once daily combined with mycophenolate mofetil (MMF) and corticosteroids. In addition to this IS treatment, she had a triple therapy of antiretrovirals (Rilpivirine, Lamivudine, and Raltegravir), a bronchodilator (Salbutamol), an antihypertensive calcium channel blocker (Amlodipine), rapid and slow insulin therapy and vitamin supplementation (**Table 1**). The blood dosing of Tac at the Department of Pharmacovigilance shown a residual concentration (CO) at 7.0 ng/ml, the therapeutic range of Tac when it is combined with MMF is 5.0-8.0 ng/ml [4]. Her previous COs for the same dosage were 6.1, 6.4, and 7.4 ng/ml, respectively (All in therapeutic range, **Figure 1**). On June 15th, 2020, due to the lack of availability of the prolonged formulation (ER-Tac once a day) of tacrolimus (Advagraf) at the hospital. Her physician has replaced him with an IR-Tac twice a day dose formulation at an equivalent dosage (1: 1) of 2.5 mg/day (1.5 mg in the morning and 1.0 mg in the evening) **(Figure 1)**. Once the steady-state was attained, another check was carried out on June 24th, 2020, who showed a C0 at 11 ng/ml. One week later, the C0 remained supratherapeutic at 12.7 ng/ml. The evolution of the C0 as a function of time is shown (**Figure 1**). This increase in Tac concentration (Co) coincided with a disturbance of the biological parameters: Blood creatinine, triglycerides and a decrease in renal creatinine clearance (**Table 2**). It should be noted that there was no drug interaction or any pathological condition that could increase Tac concentrations and hepatic function (elimination pathway and metabolization of Tac) was correct (**Table 2**). In order to effectively optimize the dosage, an AUC0 → 12.0 hrs. calculated by the Bayesian method on the platform ABIS et sites pour l'individualisation thérapeutique en transplantation CHU of Limoge was performed on June 30th, 2020, showing an overdose: AUC0 → 12h=194 ng.h/ml, therapeutic range [120-150] ng.h/ml. A dosage of 1.0 mg twice a day determined on the basis of AUC has been proposed. Subsequently, the C0 became in the therapeutic range (C0=7.3 ng/ml) (**Figure 1**). An ethical approval was obtained from our institute.

Table 1: Medication list

Specialty/dosage	International common denomination	Dosage
Advagraf (ER-Tac)	tacrolimus	2,5 mg once daily in the morning
Cellcept 250 mg tablet	MMF	Twice daily
Aspegic 100 mg	Acetylsalicylic acid	Once daily
Amlor 5 mg tablet	Amlodipine	Once dialy
Tardyferon B9	Sulfate ferreux-acide folique	Twice daily
Sterogyl H	Ergocalciférol	One every 6 months
Vitamin B12	Cobalamin	One injection IM per month
Calciforte 500:	Gluconate de calcium	Once daily
Edurant 25 mg table	Rilpivirine	Once daily
Lamivudine Mylan 300 mg	Lamivudine	Once daily
Isentress : 400 mg	Raltégravir	Twice daily
Ganfort	Bimatoprost-timolol	a drople in the evening during 6 months
Vitamin A: ophthalmic ointment	Rétinol – lanoline	One application in the evening
Ventolin aero 200	Salbutamol	2 puffs in case of crisis
Inovaire	Beclomethasone-formoterol	Two tablets per day in the morning
Doliprane 500 mg	Paracetamol	03 tablets/day
Efferaglagan codéine	Paracetamol –codeine	01 tablets*2/day
Movicol	Macrogol	03 tablets/day
Stilnox 10 mg	Zolpidem	01 Tablet in the evening
Levimir	Insulin detemir	10 IU in the evening
Actrapid	Insulin human	10 IU twice a day

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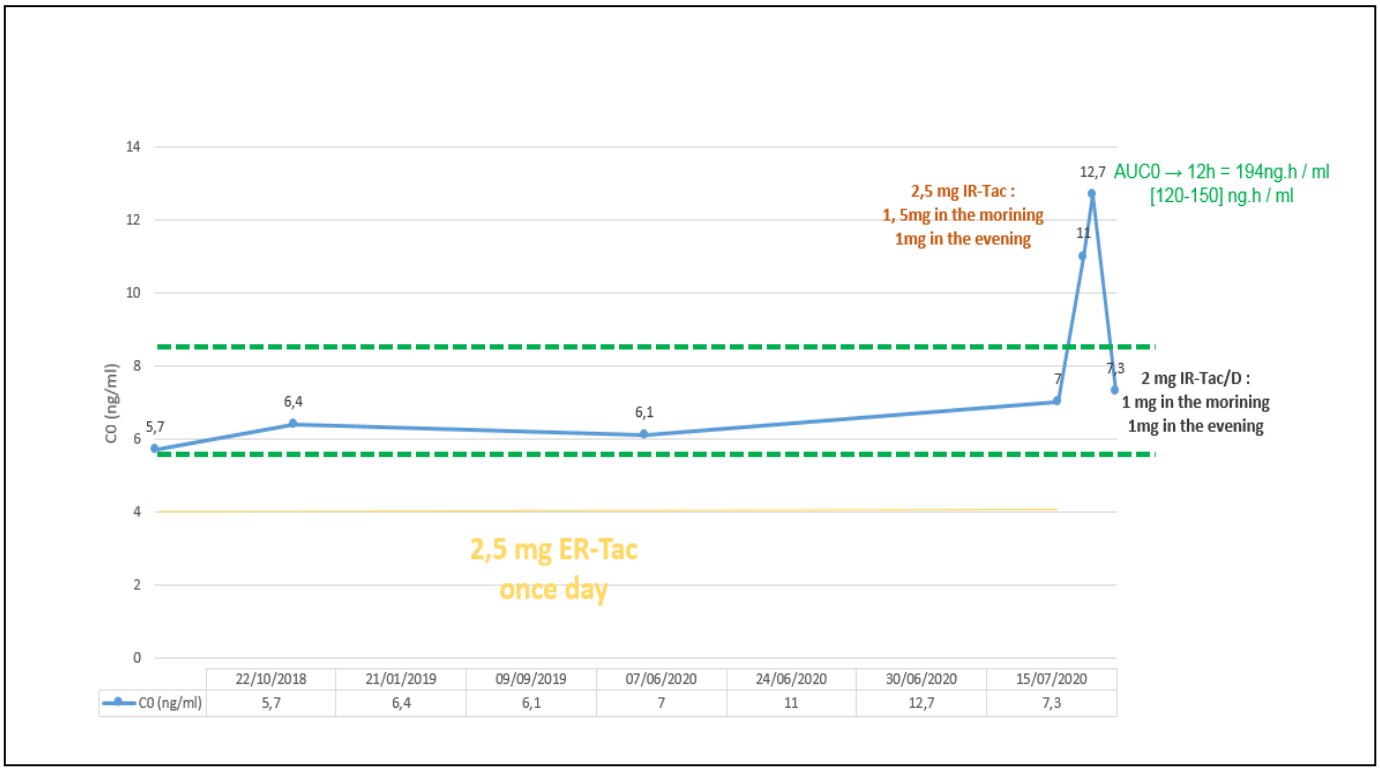

Figure 1: TDM of Tac results: C0 evolution as a function of time

Results and discussion

Tacrolimus, a calcineurin inhibitor, remains a mainstay of the treatment for rejection prophylaxis post liver transplantation. To improve adherence and reduce intra- and inter-individual variability, the TAC Extended Release (Advagraf) a once-a-day formulation, is the most widely used in LT [5, 6]. In the literature, several conversion studies from IR-Tac twice a day formulation to ER-Tac once a day formulation have been documented in adult stable kidney [7] and liver [8] transplants and in stable pediatric liver transplant recipients [9] who were converted on an mg: mg basis from twice daily TAC to a single morning dose of the ER-Tac formulation. All these studies have shown that the conversion to the ER-Tac one dose is safe and effective. However, to the best of our knowledge, there is no clinical data about the conversion from the ER-Tac once daily dose to the IR-Tac twice daily dose. In this patient, the conversion of the form the ER-Tac once a day to the IR-Tac twice a day (1.0 mg: 1.0 mg) resulted in an overdose of tacrolimus (C0 to 11.0 and 12.7 ng/ml). Since the latter is nephrotoxic [10] and can cause hypertriglyceridemia [11], this dosage could be responsible for the slight increase in creatinine; therefore, a decrease in renal clearance and an increase in triglycerides were observed (**Table 2**). To prevent the risk of Tac toxicity, to quickly and efficiently optimize the dosage and possibly to correct the observed biological disturbances, we suggested that the patient perform an AUC0 → 12.0 hrs. calculated by Bayesian methods on the platform ABIS et sites pour l'individualisation thérapeutique en transplantation CHU of Limoge by taking three samples: C0, CI, and C3. The results have also shown a supratherapeutic AUC at AUC0 → 12 hrs.=194 ng.h/ml. Dosage adjustment according to AUC0 → 12 hrs. allowed the residual concentration to be located within the therapeutic range (Co=7.3 ng/ml).

Conclusion: Through this case report, we have demonstrated the role of therapeutic drug monitoring in securing and managing the conversion from extended-release once-day dose formulation (Advagraf) to immediate-release twice-day dose Tac formulation (Prograf). When substituting Advagraf with Prograf, C0 monitoring should be regular and close, and dosage adjustments should be made to ensure that a similar systemic exposure is maintained.

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Table 2: Biological parameters

Parameters (unit)	Results June 09th, 2020	Results June 20th, 2020	Norms
Glycemia (mmol/L)	7.3	08.67	3.8-5.8
Hb A1c (%)	-	08,10	4-6
blood creatinine (mg/l)		14,36	6-12
Total bilirubin/conjugate (µmol/l)	09/04	05,3/2,57	<17/<06
ASAT/ALAT (U/l)	22/14	22,8/16,4	<35
GGT(U/l)	24	22,9	<36
PAL (U/l)	148	126	56-152
Total cholesterol (g/l)	-	1.92	<2.00
Triglycerides (g/l)	-	2.36	<1.50
Creatinine clearance (ml/min)		50.68	

HbA1c: A hemoglobin $A1_C$; ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase; GGT: gamma-glutamyltransferase; PAL: phosphatase alkaline.

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